Current and potential future role of PSMA-PET in patients with castration-resistant prostate cancer

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Abstract: PURPOSE: To review the current literature and discuss potential future roles of the novel positron emission tomography (PET) tracers targeting the prostate-specific membrane antigen (PSMA) in patients with castration-resistant prostate cancer (CRPC). METHODS: A literature search on February 19th 2018 was conducted using the Medline database and www.clinicaltrials.gov . Additionally, illustrative cases of CRPC patients from our own institution who were restaged and treated based on PSMA-PET scan results are provided. RESULTS: 11 Studies met the inclusion criteria. PSMA-PET detected more metastatic lesions compared to conventional bone scan. Several patients were up-staged from non-metastatic CRPC (nmCRPC) to metastatic CRPC (mCRPC). Currently, no clear consensus exists regarding treatment response assessment in PSMA-PET scans for mCRPC patients undergoing treatment. Also, the role of PSMA-PET as a gatekeeper for systemic therapy or radioligands is currently undefined. PSMA-guided metastasis-directed radiotherapy may not only alleviate local symptoms but has the potential to defer systemic treatment in patients with oligoprogressive CRPC. CONCLUSION: Compared to bone scan, PSMA-PET is more sensitive and specific to detect metastases but the therapeutic consequences of PSMA-PET results in the setting of CRPC remain unclear. Until future studies define the role of PSMA-PET in patients with CRPC, the current standard for imaging remains bone scan and computerized tomography.

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none

ABSTRACT

Purpose

To review the current literature and discuss potential future roles of the novel positron emission tomography (PET) tracers targeting the prostate specific membrane antigen (PSMA) in patients with castration resistant prostate cancer (CRPC).

Methods

A literature search on February 19th 2018 was conducted using the Medline database and www.clinicaltrials.gov. Additionally illustrative cases of CRPC patients from our own institution who were restaged and treated based on PSMA-PET scan results are provided.

Results

11 studies met the inclusion criteria. PSMA-PET detected more metastatic lesions compared to conventional bone scan. Several patients were up-staged from non-metastatic CRPC (nmCRPC) to metastatic CRPC (mCRPC). Currently no clear consensus exists regarding treatment response assessment in PSMA-PET scans for mCRPC patients undergoing treatment. Also the role of PSMA-PET as a gatekeeper for systemic therapy or radioligands is currently undefined. PSMA-guided metastasis-directed radiotherapy may not only alleviate local symptoms but has the potential to defer systemic treatment in patients with oligoprogressive CRPC.

Conclusion

Compared to bone scan, PSMA-PET is more sensitive and specific to detect metastases but the therapeutic consequences of PSMA-PET results in the setting of CRPC remain unclear. Until future studies define the role of PSMA-PET in patients with CRPC, the current standard for imaging remains bone scan and computerized tomography.

Keywords: Prostatic Neoplasms, CRPC, Positron Emission Tomography Computed Tomography, review, (68)Ga-PSMA

INTRODUCTION

The introduction of the new positron emission tomography (PET) tracers targeting the prostate specific membrane antigen (PSMA) in combination with cross-sectional imaging modalities, namely magnetic resonance imaging (MR) or computerized tomography (CT), is changing the treatment landscape of prostate cancer (PC) dramatically. In patients with biochemical recurrence after radical prostatectomy or radiotherapy, PSMA PET/CT showed promising detection rates of 58% and 76% for PSA ranges of 0.2-1 and 1-2 ng/mL respectively [1]. Therefore, current guidelines recommend PSMA-PET-CT for early detection of recurrence to allow targeted salvage treatment options [2].

Despite a growing body of evidence demonstrating the diagnostic superiority of PSMA-PET compared to CT or MRI and bone scan to identify metastases, the therapeutic consequences of PSMA-PET for staging in localized PC remains unclear. Conventional cross sectional imaging has a very limited sensitivity [3], since up to 80% of the lymph node metastasis are smaller than the recommended cut-off for pelvic lymph nodes of 8 mm [4]. PSMA-PET has been shown to detect metastases < 8mm resulting in a significantly higher sensitivity to detect lymph node [5] and bone metastases [6]. However, the therapeutic consequences for patients with localized prostate cancer and small PSMA-PET positive lesions remains unclear and is currently investigated, for example in the ongoing ProPSMA study (Australian New Zealand Clinical Trials Registry 12617000005358). As a consequence, current guidelines still recommend cross sectional imaging either by CT or MR and a bone scan in patients with primary diagnosis of intermediate to high risk PC [2].

In patients with castration-resistant PC (CRPC), cross sectional imaging by either CT or MR and bone scan are still the recommended staging modalities (Table 1) [7-9]. As a consequence,

most clinical trials for patients with CRPC currently require staging with cross sectional imaging by either CT or MR and bone scan [10-17]. Bone scans are widely available at low costs, but only a 2-dimensional (2D) assessment is provided routinely [18]. It can be enhanced with a detailed 3-dimensional (3D) acquisition in combination with CT for exact anatomic localization and improved characterization using single photon emission tomography with CT (SPECT/CT) [19]. However, costs and time for whole body SPECT/CT are higher, compared to standard bone scans.

The introduction of PSMA-PET for patients with CRPC as a staging modality may provide higher sensitivity/specificity and 3D lesion localization compared to CT or MRI and bone scan, but also raises many questions. First, a higher sensitivity would result in a shift from men who were previously found to have non-metastatic castration resistant (nmCRPC) according to bone scan into a metastatic CRPC (mCRPC) disease state, which would influence treatment decision making, resulting in earlier treatment and, second, exclude certain treatment options. Third, PSMA-PET would alter the definition of response to treatment and disease progression. Fourth, 3D anatomical lesion assessment would allow metastasis-directed therapy for oligometastatic CRPC.

The aim of this review was to give an overview of the potential future role of PSMA-PET in patients with CRPC in the current literature and to provide patients examples from our own experience.

METHODS

We conducted a literature search on February 19th 2018 using the Medline database and www.clinicaltrials.gov. For our literature research, we used combinations, synonyms and related search terms to “castration resistant prostate cancer” and “PSMA PET”. The following

search terms were used: prostate AND PET AND PSMA AND ("castration resistant" OR CRPC OR abiraterone OR enzalutamide OR docetaxel OR cabazitaxel). Non-English literature, animal studies, case reports, reviews, congress abstracts and correspondence/letters were excluded. Only studies reporting the diagnostic use of PSMA in PET were included. Two authors (CDF and IAB) independently screened the title and abstract of citations. The full texts of potentially eligible publications were obtained and disagreements were resolved by discussion. The reference lists of retrieved manuscripts were also screened for further eligible publications.

To provide examples of potential roles of PSMA-PET in patients with CRPC, we identified CRPC patients who were restaged with a PSMA-PET at our institution between 04/2016 and 03/2018. Informed consent was obtained from all patients and the study protocol was approved by the Cantonal Zurich Ethics Committee (metaPROC Study KEK-ZH-No. 2014-0007).

RESULTS AND DISCUSSION

Eligible studies

The initial search identified 57 studies of which eleven cohort studies that were published between 2015 and 2017 met the inclusion criteria (Table 2). One suitable study was excluded because the cohort was not described sufficiently [20].

PSMA-PET as staging procedure

The introduction of PSMA-PET challenges the sensitivity/specificity of bone scan and leads to an earlier detection of metastases, which may trigger earlier treatment. We identified 4 published studies comparing bone scan with PSMA-PET in CRPC cohorts. Pandit-Taskar et al. compared an antibody targeting PSMA (^{89}Zr-J591), with FDG-PET, bone scan and cross-sectional imaging in 50 patients with CRPC of which 34 patients were also biopsied [21]. The lesions detected by PSMA-PET and bone scan had a concordance of 89%. No overlap was observed in 236 lesions of which 189 were PSMA-PET positive and bone scan negative and 37 PSMA-PET negative but bone scan positive. Of 22 biopsied bone lesions, PSMA-PET correctly identified 18/19 metastases and 2/2 non-metastatic sites. Of 25 biopsied soft tissue sites, PSMA-PET correctly identified 14/22 metastatic sites.

Rowe et al. included 8 CRPC patients and compared bone scan and PET with a ^{18}F labeled small molecule (^{18}F-DCFBC) targeting PSMA [22]. The estimated proportion of all detected metastatic lesions that would be positive with PSMA-PET but negative or equivocal with bone scan was 0.31 (95% CI 0.14-0.57). The estimated proportion of lesions that would be positive on bone scan but negative or equivocal on ^{18}F-DCFBC PET was 0.09 (95% CI 0.05–0.17). A similar study from the same institution looking at the detections rate of ^{18}F-DCFBC PET for staging and response assessment is currently ongoing (NCT02856100). Next, Pyka et al.

compared the first ^{68}Ga labeled PSMA targeting PET tracer (^{68}Ga-PSMA-11) with bone scans in a cohort of 126 patients including 40 patients with advanced CRPC [6]. Both, PSMA-PET and bone scans identified all patients as mCRPC. As no biopsies were performed, the authors used a best valuable comparator and concluded that PSMA-PET compared to bone scans showed a significantly higher discriminatory accuracy (AUC of 0.993 vs. 0.945 $p < 0.001$). Compared to conventional cross-sectional imaging PSMA PET has a superior sensitivity for lymph node and bone metastasis. In summary, although all four studies reported that PSMA PET has a superior sensitivity for lymph node and bone metastasis, only one study [21] evaluated the diagnostic accuracy of PSMA PET with histological confirmation.

PSMA-PET as a triage tool for CRPC treatment options

PSMA-PET may not only trigger earlier treatment but might also be useful to triage the various treatment options for patients with mCRPC. The ALSYMPCA trial, which led to the approval of 223-Ra-dichloride included only patients with two or more bone metastases and no known visceral metastases according to bone scan and cross-sectional imaging [23]. If PSMA-PET instead of bone scan would be used as a staging tool for CRPC, the detection of visceral metastases will probably be higher compared to conventional imaging including CT or MRI and bone scan. As 223-Ra-dichloride is only approved for patients with mCRPC with the above mentioned inclusion criteria, newly detected metastases may prohibit patients to receive 223-Ra-dichloride (see Case 1). For example, in the study of Brauer et al. 27 mCRPC patients with bone-only metastases according to bone scan turned out to harbor visceral metastasis in 15% when a PSMA PET scan was performed [24]. Similar results were reported in a Chinese patient population [25].

Case 1: 75 year old man with CRPC and known lymph node and bone metastases undergoing restaging with PSMA PET because of a rising PSA (252 ng/ml). On coronal (A) maximum

intensity projection disseminated intense uptake in the entire skeleton is visible. Axial CT images show the extensive sclerosis (B), corresponding to increased uptake on the fused PSMA PET/CT (C). A minimally enlarged suprarenal gland on the left would probably not have been reported as suspicious lesion on CT (yellow arrow) (D), however the intense PSMA accumulation suggested suprarenal gland metastasis (E).

Furthermore, PSMA-PET may serve as a triage tool for radioligand therapy. For example Ahmadzadehfar et al. suggested that patients who were staged with PSMA-PET-CT before 223-Ra-dichloride were more likely to respond compared to patients without prior PSMA-PET-CT [26]. Although this represents an interesting hypothesis, this trial used PSA response as the only outcome and the different response between the groups could be caused by confounders alone.

While 223-Ra-dichloride is active in all sclerotic osseous sites, PSMA-targeting molecules might only be active in PSMA-expressing tumors. PSMA-PET is currently used to select patients for ^{177}Lu-PSMA therapy in most centers, with high PSMA expression in the metastasis being the most important selection criterion for internal radiotherapy[27,28]. Therefore, another hypothesis would be that PSMA-PET should predict treatment response to PSMA-targeting molecules. However this hypothesis was not confirmed by Ferdinandus et al., who reported that several clinicopathological variables but no single PSMA-PET obtained variable was predictive for PSA response during ^{177}Lu-PSMA therapy [29]. Overall, PSMA seems to be an interesting tool to improve treatment selection in CRPC. However future studies are necessary to elucidate if treatment selection according to PSMA-PET scan results will translate into survival benefits.

PSMA-PET for response assessment

The best established and widely accepted criteria for treatment response assessment in cancer are the response evaluation criteria for solid tumors (RECIST) [30]. Sonpavde et al. could show that progressive disease on CT based on RECIST is prognostic for patients with metastatic PC [31]. However, RECIST is of limited use for PC, since bone lesions can be considered as target lesions, only if they have a soft tissue component of > 1 cm, and lymph nodes need a short axis diameter of > 1.5 cm. To further incorporate bone scan results, the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) published a modified response assessment recommendation including RECIST 1.1 based on CT or MRI and bone scans [8]. Because a more sensitive and specific diagnostic tool like PSMA-PET may alter response assessments substantially, further studies defining the role of new PET-tracers for response assessment in patients with CRPC are of utmost importance.

Guidelines for the use of PET for response assessment only exist for FDG, the most widely accepted criteria are the EORTC recommendations from 1999 and the PET Response Criteria in Solid Tumors (PERCIST), that are closely related to RECIST [32]. FDG accumulation in solid tumors is a measure for metabolic tumor activity and therefore a good tool to assess response to therapy. PSMA PET on the other hand is targeting the transmembranous protein PSMA. Little is known about the effect of treatment on the regulatory mechanisms of PSMA expression. First in vitro results of our institution show that exposure of PC cell lines to anti-androgen therapy in fact increases PSMA expression [33]. Therefore, careful evaluation of PSMA PET for treatment response assessment regarding time point of imaging and also selection of the best representative measure will be necessary.

Only one study reported the results of PSMA-PET-CT scans before and after 3 cycles of docetaxel in 16 men with CRPC [34]. The authors compared PSA response with either response

on PSMA-PET or on CT scans. Outcome prediction was concordant between PSA response and PSMA-PET results in nine of 16 patients (56%) but only in four of 12 patients (33%) when assessed by CT.

PSMA-PET may also represent a gatekeeper for 223-Ra-dichloride treatment and serve as a promising response assessment tool for radioligand therapy. Although the ALSYMPCA trial demonstrated an overall survival benefit, many clinicians and patients are concerned about rising PSA values during treatment with Ra-223-dichloride. PSMA-PET based response assessment during radioligand therapy may offer an objective assessment tool, which may help to observe treatment response despite rising PSA levels and calm clinicians and patients.

This hypothesis was supported in the reviewed literature by Ahmadzadefar et al., who argued that PSMA-PET-CT could represent not only a better tool for patient selection as discussed above, but also superior to PSA to assess treatment response after Ra-223-dichloride [26]. In a cohort of patients with CRPC undergoing 223-Ra-dichloride treatment, Bieth et al. identified 31 patients who had PSMA-PET and bone scan respectively. Whereas bone scans were used to calculate the bone scan index (BSI), the authors used PSMA-PET-CT images to calculate two new indices incorporating the percentage of bone volume (BPI_{VOL}) and average SUV (BPI_{SUV}). Because of the limited sample size and lack of clinical endpoints those developments have to be validated in future studies. Therapy response assessment with PSMA PET might help to assess response in selected situations. However, careful evaluation of different drug effects on tracer expression will be necessary for integration of PSMA expression into response assessments.

PSMA-PET targeted local and metastasis-directed therapy in the oligoprogressive CRPC patient

Encouraging results of local or metastasis-directed therapy in patients with hormone-naïve oligometastatic recurrent PC [35,36] raise the question if oligoprogressive mCRPC patients may also benefit from local and/or metastasis-directed therapy [37-39]. Although it remains unclear if oligoprogressive CRPC patients represent a distinct biological entity or whether the PSMA-positive lesions are just a snapshot of a systemic disease, the improved sensitivity resulting in an earlier detection and the 3D localization of oligoprogressive disease may offer a window of opportunity. In the study of Guler et al., 10 CRPC patients treated with intensity-modulated and image-guided radiotherapy showed a progression free survival (PFS) of 0% at 12 months [40]. Similarly Muldermanns et al. reported a biochemical PFS of 54% and a distant PFS of 45 % at 16 months [39]. For CRPC patients with progressive disease in the locally untreated prostate, Aizawa et al. showed that radiotherapy of the prostate can achieve al long-term effect with a 8year clinical failure-free survival of 51% and a 8year relapse-free-survival of 26% by treatment of the pelvis [41]. Median duration to recurrence after RT was 19 months. Local relapse free survival was 91% after 8 years. Overall, PSMA-PET targeted radiotherapy in oligoprogressive mCRPC is still controversial and needs further investigation. Our cases 2-4 illustrate the concept of target-directed therapy in patients with oligoprogressive mCRPC.

While delaying exposure to systemic therapy in patients with CRPC reduces the exposure of patients to treatment-related toxicity, and from a payer perspective delays expensive systemic therapies, it is still unknown whether this translates into a clinical benefit for patients (i.e. quality of life, overall survival). Indeed, local and metastasis-directed therapy in the oligoprogressive CRPC patient might even be harmful by postponing the use of systemic treatments. Therefore, image-guided therapies should be used as adjuncts rather than being used instead of systemic treatment.

Case 2: Example of PSMA-PET targeted metastasis-directed therapy in the oligoprogressive setting: History of radical prostatectomy 2006 and salvage radiotherapy 03/07 with 66 Gray. He received ADT from 03/13 to 03/16, with a rise in PSA from 0.9 ng/ml (07/15) to 6.7 ng/ml (02/16). On coronal (A) and sagittal (B) maximum intensity projection of PSMA PET (06/16) a focal uptake in the third lumbar vertebra is seen. Fused axial PET/CT images shows the increased uptake (C), corresponding to a focal sclerosis (D, yellow arrow). Note that a second sclerotic lesion in the 8th thoracic vertebra was PSMA negative (E), despite dense sclerosis on CT (F, green arrow). Stereotactic body radiotherapy with 48.5 Gray in 10 fractions to the PSMA positive bone lesion was performed without additional systemic treatment and until now, 15 months later, the PSA is unmeasurable. This case does not only illustrate the high tumor to back ground ratio of PSMA PET for bone lesions, but also the superior specificity compared to CT and the potential of PSMA-guided metastasis-directed therapy in the CRPC setting.

Case 3: Example of PSMA-PET targeted metastasis-directed therapy in the oligoprogressive setting: A 70 year old patient with CRPC since 12/2016. History of a robot-assisted laparoscopic radical prostatectomy of a pT2c cN0 cM0 Gleason 4+3=7b R0 resected prostate tumor. Postoperative, a serum PSA nadir of 0.4ng/ml was reached 6 weeks after prostatectomy. With serum PSA-levels rising to 0.63ng/ml, a robot-assisted laparoscopic pelvic lymphadenectomy was performed in 2009 (pN0). In 2014 the serum-PSA-level rose to 37.2ng/ml. A Choline-PET showed bone- and lymph node metastases (A). An antiandrogen therapy with Goserelin was started 06/2014. In 06/2016, PSA-levels started to rise despite Goserelin, and a CRPC-status was reached in 12/2016. In 11/2017, at a PSA-level of 3.8ng/ml, PSMA-PET-CT was performed, that showed a recurrence of the bone metastasis in the right

pubic bone, but no other metastases (B-D). A stereotactic radiotherapy to the bone metastasis was performed with 30 Gy in 5 fractions(E). Three months after treatment, the PSA-level was reduced to 1.4ng/ml. This case illustrates the accuracy of PSMA-PET showing active metastases, and gives an example of how oligoprogressive lesions can be locally irradiated to postpone second line systemic therapy.

Case 4: Example of PSMA-PET targeted therapy of the oligoprogressive primary tumor in the CRPC-setting: A 70 year old patient with CRPC since 07/2016. First diagnosis of synchronous metastatic cT3b cN1 cM1 Gleason 4+5=9 prostate cancer, with bone and lymph node metastases in 05/2015. The serum PSA at first diagnosis was 332 ng/ml. A Choline-PET (A) showed multiple pelvic lymph node metastases and bone metastases. The patient received leuprorelin and reached a PSA-Nadir of 15 ng/ml in 12/2015. In the following year PSA rose again. On PSMA-PET in 09/16 the lymph node and bone metastases still showed a good response without any PSMA-expression. The prostate however, showed intense PSMA-accumulation (B). The patient was observed until PSA rose to 27 ng/ml and a new PSMA-PET (C-E) demonstrated still only a PSMA-PET avid local prostate cancer, without any activity in the previous bone- and lymph node metastases sites. The prostate and seminal vesicles were irradiated with 76.2Gy in 33 fractions in 10/2017 (F) and 3 months later, PSA dropped significantly to 1.21 ng/ml. The patient experienced no side effects of the irradiation. This is an interesting example of an oligoprogressive CRPC patients in which potentially only the primary tumor became resistant to ADT.

CONCLUSION

The improved sensitivity and specificity of PSMA-PET to detect metastases has the potential to change the treatment landscape of patients with CRPC dramatically. The current literature provides mostly retrospective, small cohort studies with clinically questionable outcomes. Therefore, further studies are urgently needed to verify if the introduction of PSMA-PET will result into improved outcomes. Until further data is available, conventional imaging including CT or MRI and bone scan remains the gold standard for patients with CRPC.

Authors' contribution to the Manuscript.

CD Fankhauser: Protocol/project development, Other (Literature research), Manuscript writing/editing
C Poyet: Manuscript writing/editing
B Kranzbühler: Manuscript writing/editing
SGC Kroeze: Manuscript writing/editing
H Garcia: Manuscript writing/editing
PA Kaufmann: Manuscript writing/editing
M Guckenberger: Manuscript writing/editing
T Hermanns: Manuscript writing/editing
Burger IA: Protocol/project development, Manuscript writing/editing

Data collection or management
chose from: Protocol/project development
Data analysis
Manuscript writing/editing
Other (please specify briefly using 1 to 5 words)

Compliance with Ethical Standards

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Table 1 Current guideline and consensus recommendations regarding imaging for patients with castration resistant prostate cancer

Guideline	Recommended imaging modality
EAU/ESTRO/ESUR/SIOG 2018	Bone scan and CT of chest abdomen and pelvis
NCCN 2018	"…chest CT, bone imaging, and abdominal CT or MRI with or without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 fluciclovine PET/CT or PET/MRI for further soft tissue evaluation or F-18 sodium fluoride PET/CT for further bone evaluation.
APCCCP 2017	"…74% of the panel voted for CT and bone scintigraphy and 24% of the panellists voted for one of the next generation imaging methods." "For monitoring of patients with a diagnosis of aggressive variant mCRPC, 62% of the panellists voted for standard imaging by CT and bone scintigraphy, 2% voted for CT alone, and 36% voted for next-generation imaging modalities."

Table 1 Summary of included studies

Author or ClinicalTrials.gov Identifier	Year	Sample Size	Results	Limitations	PSMA tracer
PSMA as staging procedure					
Pandit-Taskar [1]	2015	50	Lesions detected by PSMA-PET and bone scan had a concordance of 89%. No overlap was observed in 236 lesions of which 189 were PSMA-PET positive and bone scan negative and 37 PSMA-PET negative but bone scan positive. Of 22 biopsied osseous sites, PSMA-PET correctly identified 18/19 metastases and 2/2 non-metastatic sites. Of 25 biopsied soft tissue sites, PSMA-PET correctly identified 14/22 metastatic sites	Limited number of biopsied metastases	^{89}Zr-J591
Rowe [2]	2016	8	The estimated proportion of all detected metastatic lesions that would be positive with PSMA-PET but negative or equivocal with bone scan was 0.31 (95% CI 0.14-0.57) The estimated proportion of lesions that would be positive on bone scan but negative or equivocal on ^{18}F-DCFBC PET 0.09 (95% CI 0.05–0.17.	No histological confirmation	^{18}F-DCFBC
Pyka [3]	2016	40	Authors used a “best valuable comparator” and concluded that PSMA-PET compared to bone scans showed a significantly higher discriminatory accuracy (AUC of 0.993 vs. 0.945 $p < 0.001$).	No histological confirmation	^{68}Ga-PSMA-11
NCT02856100		20	Ongoing trial comparing metastatic lesions detected on PSMA-PET/CT at baseline and follow-up with standard of care conventional imaging (CT and bone scan) response at 8-12 weeks		^{18}F-DCFBC
PSMA-PET as a gate keeper					
Brauer [4]	2017	27	Bone-only metastases according to bone scan turned out to harbor PSMA avid visceral metastases in 15% of all patients	Retrospective cohort study	^{68}Ga-PSMA-11
Zang[5]	2017	15	Newly detected visceral metastasis in a subset of CRPC patients	Not clear if in the CRPC or the treatment naïve population	^{68}Ga-PSMA-11
Ahmadzadehfar [6]	2017	32	Patients who were staged with PSMA-PET-CT before 223-Ra-dichloride were more likely to respond compared to patients without prior PSMA-PET-CT	Retrospective cohort study, confounding very likely	^{68}Ga-PSMA-11
Ferdinandus[7]	2017	40	Several clinicopathological variables but no PSMA-PET obtained variables were predictive for PSA response during 177Lu-PSMA therapy	Retrospective cohort study, confounding very likely	^{68}Ga-PSMA-11

PSMA-PET for response assessment					
Seitz[8]	2017	16	Outcome prediction was concordant between PSA response and PSMA-PET results in nine of 16 patients (56%) but only in four of 12 patients (33%) when assessed by CT	Retrospective cohort study	^{68}Ga-PSMA-11
Ahmadzadefar[6]	2017	32	PSMA-PET-CT could represent a better tool then PSA to assess treatment response after Ra-223-dichloride	Retrospective cohort study	^{68}Ga-PSMA-11
Bieth[9]	2017	31	PSMA-PET-CT images were used to calculate two new indices incorporating the percentage of bone volume (BPI_{VOL}) and average SUV (BPI_{SUV})	Retrospective cohort study	^{68}Ga-PSMA-11
PSMA-PET targeted metastasis-directed therapy in the oligometastatic setting					
Guler [10]	2017	10	No recurrences at irradiated sites, progression free survival of 0% at 12 months	Retrospective cohort study	^{68}Ga-PSMA-11

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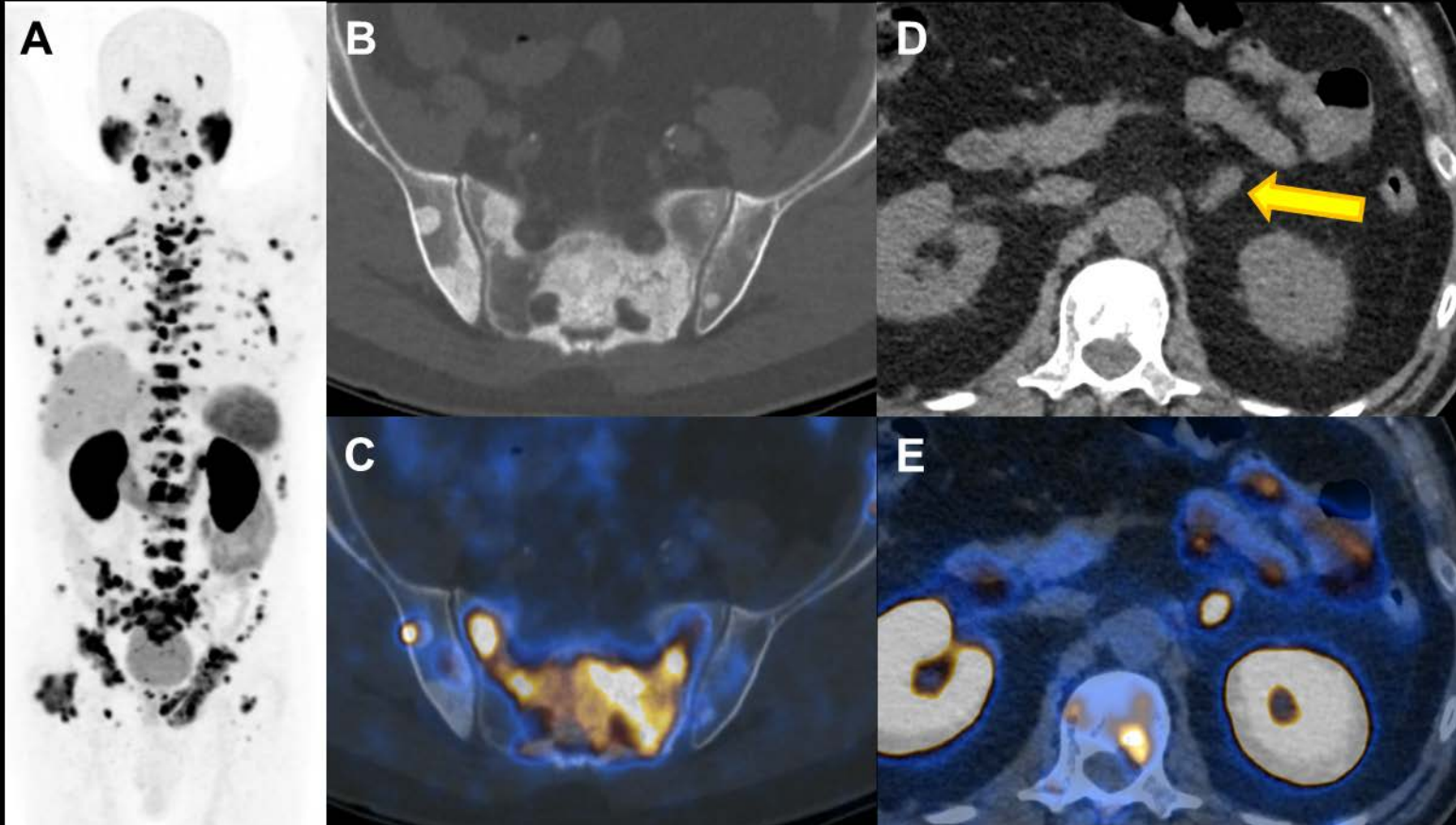
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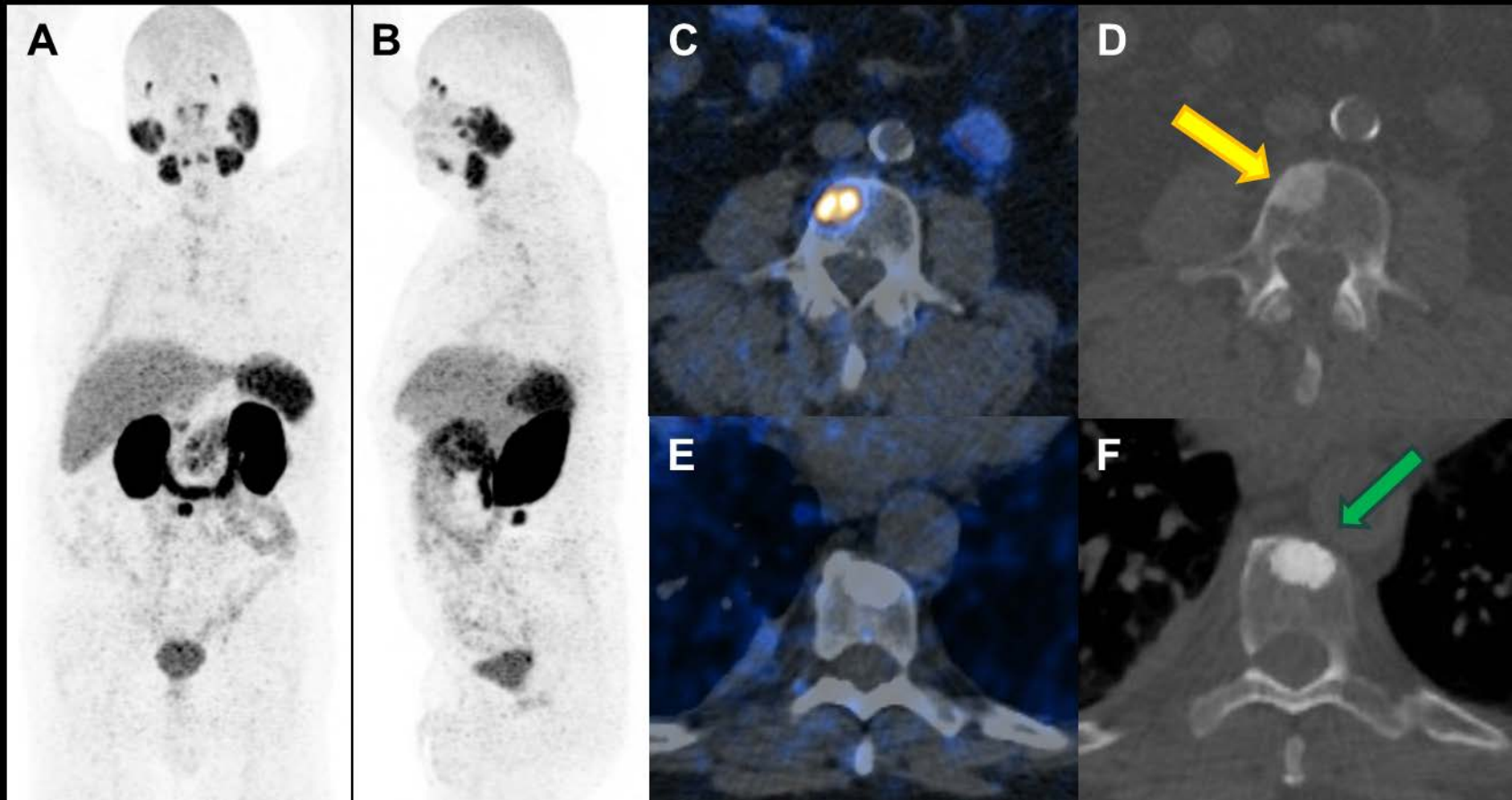
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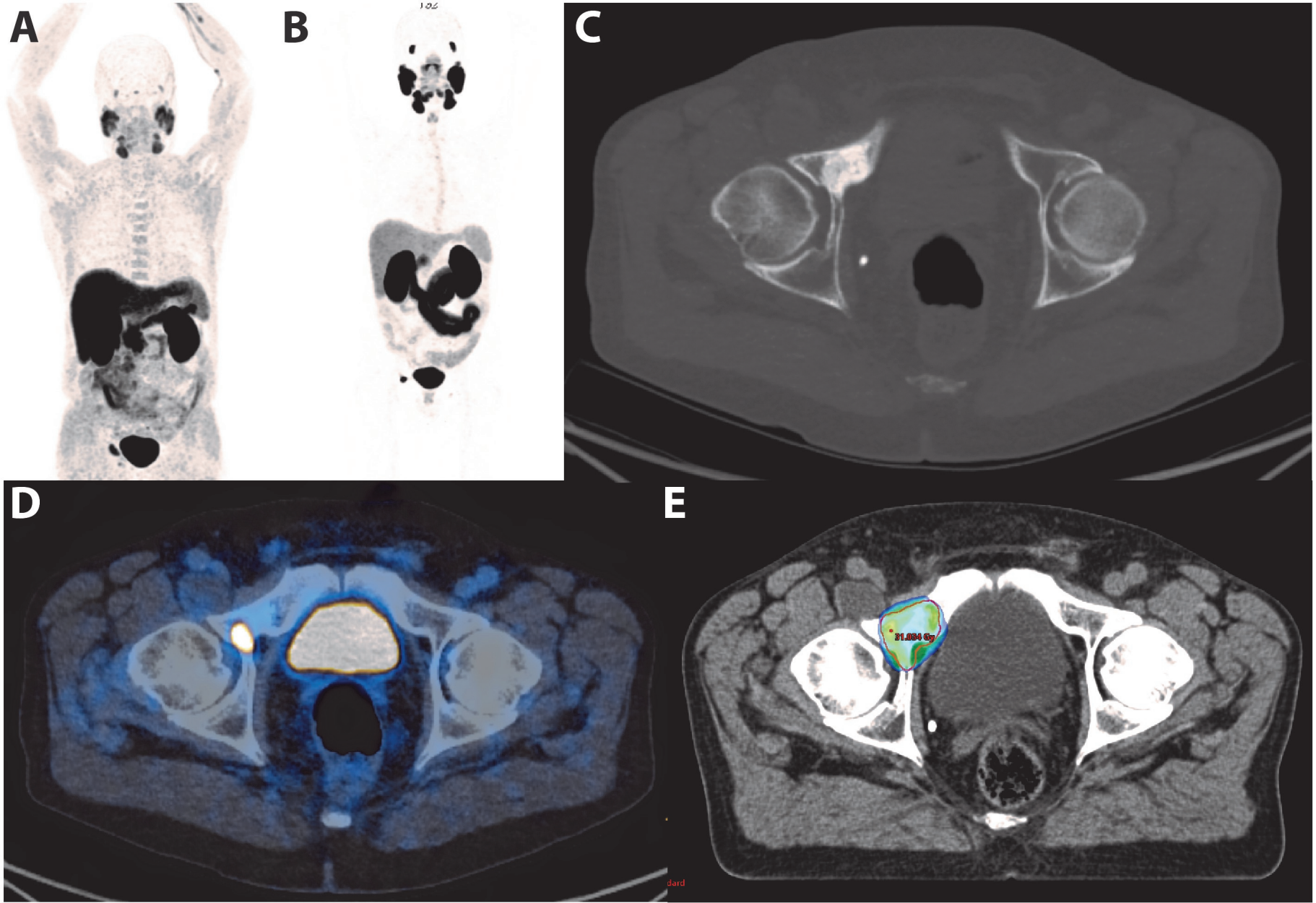
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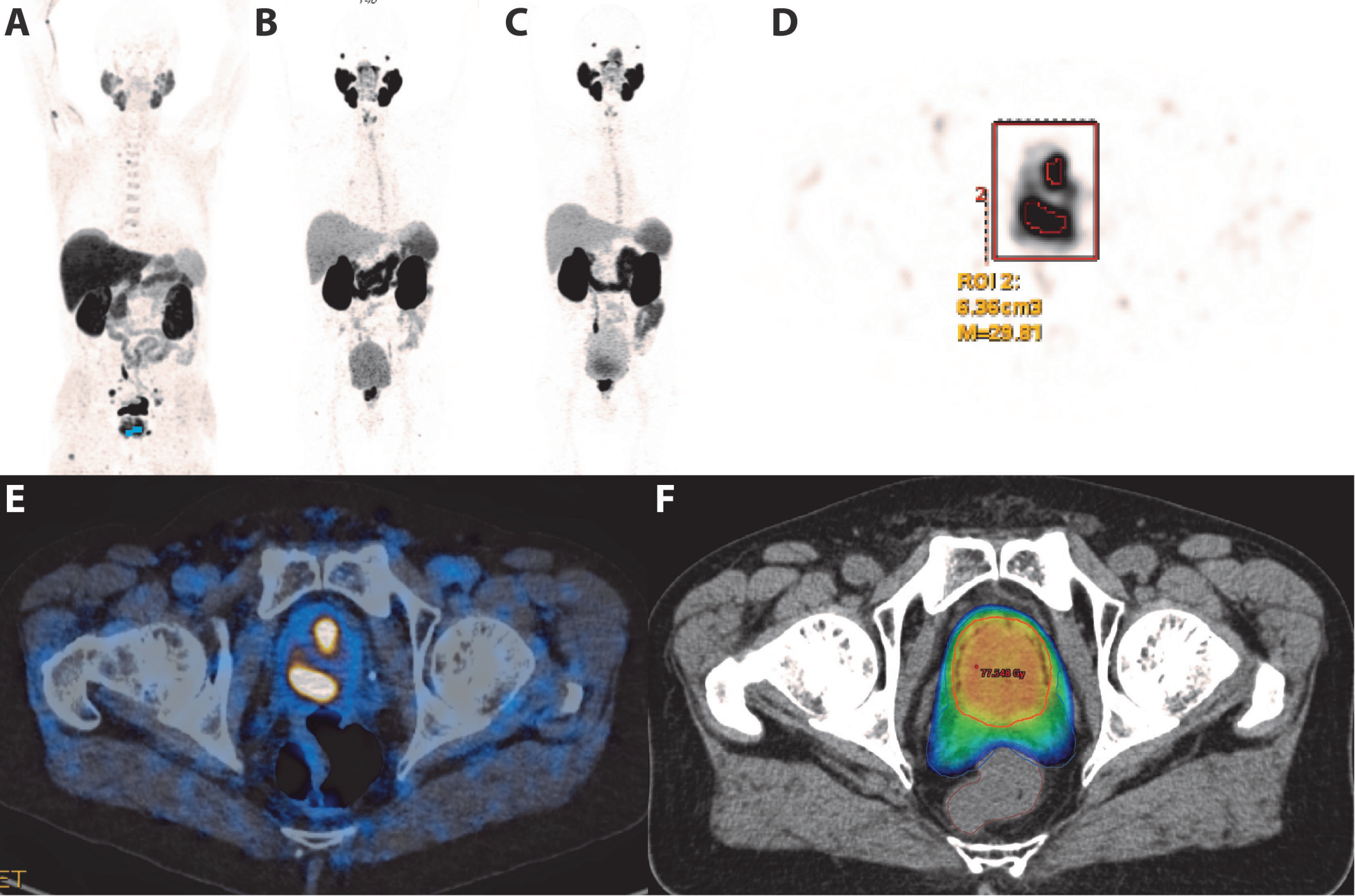
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